Amendments to the Claims

This listing of claims replaces all prior listings, and versions, of claims in the application.

Listing of Claims

1 - 271. (canceled)

272. (currently amended) A method of identifying an agent that modulates a phenotype associated with a disruption of a gene which encodes for a PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a phenotype resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the test agent modulates the identified phenotype associated with gene disruption in the non-human transgenic animal.

273. (currently amended) The method of Claim 272, wherein the phenotype associated with the gene disruption comprises ~~a neurological disorder,~~ a cardiovascular~~, endothelial or angiogenic~~ disorder; or an eye abnormality~~; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality~~.

274-279. (canceled)

280. (previously presented) The method of Claim 273, wherein the eye abnormality is a retinal abnormality.

281. (previously presented) The method of Claim 273, wherein the eye abnormality is consistent with vision problems or blindness.

282. (previously presented) The method of Claim 280, wherein the retinal abnormality is consistent with retinitis pigmentosa.

283. (previously presented) The method of Claim 280, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

284. (previously presented) The method of Claim 280, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplaisa spondyloepiphysaria congentia, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie dunsdrome, Stickler syndrome, carotinemeia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

285 – 287. (canceled)

289. (currently amended) The method of Claim 273, wherein the cardiovascular~~, endothelial or angiogenic~~ disorders are arterial diseases, such as diabetes mellitus; papilledema ; optic atrophy; atherosclerosis~~; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure;~~ or hypertension~~; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e. g., hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma, haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other inj ured tissue, implant fixation, scarring;~~

~~ischemia reperfusion injury; rheumatoid arthritis; cerebrovascular disease; renal diseases such as acute renal failure, or osteoporosis~~.

289- 290. (canceled)

291. (currently amended) The method of Claim 272, wherein the non-human transgenic animal exhibits ~~at least one of~~ the following physiological ~~characteristics~~ characteristic compared with gender matched wild-type littermates: ~~a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing;~~ an increased mean artery-to-vein ratio associated with retinal degeneration~~; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level; a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge; increased mean serum IgM, IgGl, IgG2a and IgG2b levels; increased mean serum IgM, IgA and IgG3 levels; increased mean serum IgM, IgGl, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrate; a decreased mean bone mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgGl, IgG2a, IgG2b and IgG3 levels~~.

292 - 295. (canceled)

296. (currently amended) A method of identifying an agent that modulates a physiological characteristic associated with a disruption of the gene which encodes for a PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide; (b) measuring a physiological characteristic exhibited by the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic exhibited by the non-human transgenic animal that differs from the physiological characteristic exhibited by the wild-type animal is identified as a physiological characteristic associated with gene disruption; (d) administering a test agent to the non-human transgenic animal of (a); and (e) determining whether the physiological characteristic associated with gene disruption is modulated.

297. (currently amended) The method of Claim 296, wherein the non-human transgenic animal exhibits ~~at least one of~~ the following physiological ~~characteristics~~ characteristic compared with gender matched wild-type littermates: ~~a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing;~~ an increased mean artery-to-vein ratio associated with retinal degeneration~~; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level; a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge ; increased mean serum IgM, IgGI, IgG2a and IgG2b levels ; increased mean serum IgM, IgA and IgG3 levels; increased mean serum IgM, IgGl, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation ; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation ; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrate; a decreased mean bone~~

~~mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis ; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgGl, IgG2a, IgG2b and IgG3 levels~~.

298 – 312. (canceled)

313. (currently amended) A method of identifying an agent that ameliorates or modulates ~~a neurological disorder;~~ a cardiovascular~~, endothelial or angiogenic~~ disorder; or an eye abnormality~~; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality~~ associated with a disruption in the gene which encodes for a PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for a PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide; (b) administering a test agent to said non-human transgenic animal; and (c) determining whether said test agent ameliorates or modulates the ~~neurological disorder;~~ cardiovascular~~, endothelial or angiogenic~~ disorder~~;~~ or eye abnormality~~; immunological disorder; oncological disorder; bone metabolic abnormality or disorder; lipid metabolic disorder; or developmental abnormality~~ in the non-human transgenic animal.

314 – 319. (canceled)

320. (previously presented) The method of Claim 313, wherein the eye abnormality is a retinal abnormality.

321. (previously presented) The method of Claim 313, wherein the eye abnormality is consistent with vision problems or blindness.

322. (previously presented) The method of Claim 320, wherein the retinal abnormality is consistent with retinitis pigmentosa.

323. (previously presented) The method of Claim 320, wherein the retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

324. (previously presented) The method of Claim 320, wherein the retinal abnormality is consistent with retinal dysplasia, various retinopathies, including retinopathy of prematurity, retrolental fibroplasia, neovascular glaucoma, age-related macular degeneration, diabetic macular edema, corneal neovascularization, corneal graft neovascularization, corneal graft rejection, retinal/choroidal neovascularization, neovascularization of the angle (rubeosis), ocular neovascular disease, vascular restenosis, arteriovenous malformations (AVM), meningioma, hemangioma, angiofibroma, thyroid hyperplasias (including Grave's disease), corneal and other tissue transplantation, retinal artery obstruction or occlusion; retinal degeneration causing secondary atrophy of the retinal vasculature, retinitis pigmentosa, macular dystrophies, Stargardt's disease, congenital stationary night blindness, choroideremia, gyrate atrophy, Leber's congenital amaurosis, retinoschisis disorders, Wagner's syndrome, Usher syndromes, Zellweger syndrome, Saldino-Mainzer syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, Alport's syndrome, Alstrom's syndrome, Cockayne's syndrome, dysplaisa spondyloepiphysaria congentia, Flynn-Aird syndrome, Friedreich ataxia, Hallgren syndrome, Marshall syndrome, Albers-Schnoberg disease, Refsum's disease, Kearns-Sayre syndrome, Waardenburg's syndrome, Alagile syndrome, myotonic dystrophy, olivopontocerebellar atrophy, Pierre-Marie dunsdrome, Stickler syndrome, carotinemeia, cystinosis, Wolfram syndrome, Bassen-Kornzweig syndrome, abetalipoproteinemia, incontinentia pigmenti, Batten's disease, mucopolysaccharidoses, homocystinuria, or mannosidosis.

325 – 327. (canceled)

328. (currently amended) The method of Claim 313, wherein the cardiovascular~~,~~ ~~endothelial or angiogenic~~ disorders are arterial diseases, such as diabetes mellitus; papilledema; optic atrophy; atherosclerosis~~; angina; myocardial infarctions such as acute myocardial infarctions, cardiac hypertrophy, and heart failure such as congestive heart failure;~~ or hypertension~~; inflammatory vasculitides; Reynaud's disease and Reynaud's phenomenon; aneurysms and arterial restenosis; venous and lymphatic disorders such as thrombophlebitis, lymphangitis, and lymphedema; peripheral vascular disease; cancer such as vascular tumors, e. g. , hemangioma (capillary and cavernous), glomus tumors, telangiectasia, bacillary angiomatosis, hemangioendothelioma, angiosarcoma,~~

~~haemangiopericytoma, Kaposi's sarcoma, lymphangioma, and lymphangiosarcoma; tumor angiogenesis; trauma such as wounds, burns, and other injured tissue, implant fixation, scarring; ischemiareperfusion injury ; rheumatoid arthritis; cerebrovascular disease ; renal diseases such as acute renal failure, or osteoporosis~~.

329 – 330. (canceled)

331. (currently amended) The method of Claim 313, wherein the non-human transgenic animal exhibits ~~at least one of~~ the following physiological ~~characteristics~~ characteristic compared with gender matched wild-type littermates: ~~a decreased anxiety-like response during open field activity testing; an increased anxiety-like response during open field activity testing; balding, exothalamus observations, and piloerection observations in functional observation battery (FOB) testing;~~ an increased mean artery-to-vein ratio associated with retinal degeneration~~; developing cataracts; an increased mean serum cholesterol level; an increased mean serum triglyceride level; a decreased mean serum insulin level, a decreased mean percentage of B cells in the spleen and lymph node; a decreased mean serum IgG2a response to an ovalbumin challenge; decreased mean serum IgA levels; an increased mean serum IgG2a response to an ovalbumin challenge; increased mean serum IgM, IgGl, IgG2a and IgG2b levels; increased mean serum IgM, IgA and IgG3 levels; increased mean serum IgM, IgGl, IgG2a and IgG2b levels; an increased mean percentage of CD4 cells and a decreased mean percentage of CD8 cells in spleen and thymus; mobilization of neutrophils in response to peritoneal inflammation ; an enhanced DDS-induced colitis response; an enhanced ConA-induced hepatitis response; a decreased skin fibroblast proliferation; a decreased volumetric bone mineral density, a decreased bone mineral content index (BMC/LBM), and a decreased mean bone mineral density in total body, femur and vertebrate; a decreased mean bone mineral density, a decreased mean trabecular bone volume, decreased thickness, and decreased connectivity density; a decreased body weight and length, decreased total tissue mass and lean body mass, a decreased femoral midshaft cross-sectional area with decreased alkaline phosphatase levels; growth retardation with decreased body weight and length, total tissue mass, and lean body mass; a diaphragmatic hernia; an increased total tissue mass, increased lean body mass, increased bone mineral content, increased total body and increased femoral bone mineral density; an enhanced glucose tolerance; developmental disorders including abnormal kidney development marked by kidney agenesis; embryonic lethality; or embryonic lethality wherein heterozygous adults exhibited decreased serum IgM, IgGl, IgG2a, IgG2b and IgG3 levels~~.

332 – 341. (canceled)

342. (currently amended) A method of evaluating a therapeutic agent capable of affecting a condition associated with a disruption of a gene which encodes for a PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide, the method comprising: (a) providing a non-human transgenic animal whose genome comprises a disruption of the gene which encodes for the PR0224~~, PR09783, PRO1108, PR034000, PR0240, PR0943, huA33, PR0230, PR0178, PRO1199, PR04333, PR01336, PR019598, PR01083, hu TRPM2 or PR01801~~ polypeptide; (b) measuring a physiological characteristic of the non-human transgenic animal of (a); (c) comparing the measured physiological characteristic of (b) with that of a gender matched wild-type animal, wherein the physiological characteristic of the non-human transgenic animal that differs from the physiological characteristic of the wild-type animal is identified as a condition resulting from the gene disruption in the non-human transgenic animal; (d) administering a test agent to the non-human transgenic animal of (a); and (e) evaluating the effects of the test agent on the identified condition associated with gene disruption in the non-human transgenic animal.

343. (currently amended) The method of Claim 342, wherein the condition is ~~a neurological disorder;~~ a cardiovascular~~, endothelial or angiogenic~~ disorder; or an eye abnormality~~; an immunological disorder; an oncological disorder; a bone metabolic abnormality or disorder; a lipid metabolic disorder; or a developmental abnormality~~.

344 - 386. (canceled)